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(54) Title: NEW CRYSTALLINE FORMS OF CARVEDILOL

(57) Abstract: The present invention relates to new crystalline carvedilol forms VII and IX and to processes for the preparation thereof. Particularly, this invention relates to processes of the isolation of carvedilol, using ethyl acetate as a solvent.

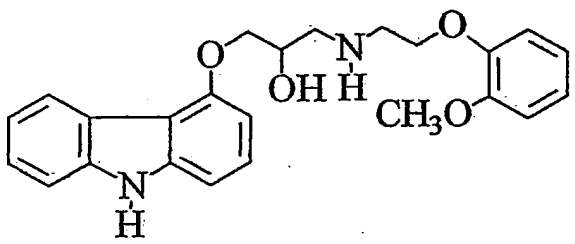
NEW CRYSTALLINE FORMS OF CARVEDILOL

Field of the invention

The invention relates to the field of physical and synthetic organic chemistry. It relates to the process for crystallization of novel solid crystalline modification of carvedilol or solvate thereof, having an excellent efficacy as pharmaceuticals.

Background of the invention

Carvedilol, (±)-1-(9*H*-carbazolyl-4-oxy)-3-[[2-(2-methoxyphenoxy) ethyl]amino]-2-propanol, is a non selective β-adrenergic blocker with α1-blocking activity. Solid drug formulations are useful in the treatment of hypertension, congestive heart failure and angina. It is used in pharmaceutical compositions as a racemic mixture of both enantiomers, having structural formula:



Carvedilol possesses colourful polymorphic behaviour. Depending to the method of isolation, several different solid crystalline modifications are identified. Several stable modifications and some stable and semi stable hydrates, solvates and salts of the drug were discovered and characterized by many development groups. The solid polymorphs, pseudo polymorphs, hydrates, solvates and salts are well analytically characterized. Materials could be successfully distinguished comparing their IR, Raman, XRPD, DSC or solid NMR spectra and melting points.

The synthesis of carvedilol is consisted from several consecutive synthetic steps. The stable solid form, used for oral pharmaceutical formulations, is isolated from ethyl acetate. The methods for the synthesis and isolation are disclosed in EP 0 004 920 B1.

EP 0 004 920 B1 discloses the isolation of carvedilol from ethyl acetate. Following the procedure, pure and stable modification II of carvedilol is isolated and characterized by melting point.

EP 0 893 440 A1 discloses the crystallization of carvedilol from methanol. Thermodynamically more stable modification I was isolated.

WO 02/00216 and WO 03/005970 describe stable modification III of carvedilol. According to the experiments disclosed in the cited applications, polymorph III could be prepared by crystallization from water or precipitation from organic solvent by addition of water used as anti-solvent.

WO 02/00216 describes also new solid modifications of carvedilol, designated as forms IV and V, which could be prepared by isolation from organic solvents with precipitation by addition of cyclohexane or hexane.

WO 03/029214 A1 describes new modification of carvedilol, which is hemihydrate and prepared by dissolving spray congealed material in water or methanol/water as crystallization media.

WO 03/059807 A2 describes a crystalline solid of carvedilol solvate, designated as form VI.

Technical problem

Appearance of organic compounds in different solid modifications is a challenging topic in pharmaceutical industry. The synthetic processes used for production, especially the isolation steps and industrial pharmaceutical processes are highly investigated. Qualitative and quantitative physical parameters of particular technological steps are elaborated and validated.

Different solid modifications of the same compound usually exhibit different properties in dissolution and bulk properties which have a significant effect to method of formulation of the solid drug and finally could effect the drug bioavailability. The active pharmaceutical ingredients isolated in processes for the synthesis and used in formulations are to be in

defined crystalline modifications, and usually with validated bulk properties, like particle size or specific surface.

Summary of the invention

In our investigation of the isolating step for the preparation of carvedilol, using ethyl acetate as a solvent, surprisingly new crystalline carvedilol forms were found. We isolated different solid crystalline modifications of carvedilol in the way that we modified concentration of the drug in ethyl acetate solution and water concentration in ethyl acetate in which the drug is dissolved and crystallized.

Brief description of the figures

Figure 1: FT-IR spectrum of crystalline form VII.
Figure 2: DSC curve of crystalline form VII.
Figure 3: XRPD pattern of crystalline form VII.
Figure 4: FT-IR spectrum of crystalline form IX.
Figure 5: DSC curve of crystalline form IX.
Figure 6: XRPD pattern of crystalline form IX.

Methods of the measurement

FT-IR spectra in KBr pellets were recorded over the wave number range of 4000-400cm^{-1} with a Paragon 1000 Perkin Elmer Spectrometer at resolution 4 cm^{-1}.

DSC scans were recorded on Perkin Elmer DSC 7 Scanning calorimeter. Samples of approx. 3 mg were scanned between 30 and 130°C at heating rate of 10°C/min under nitrogen atmosphere in aluminium DSC open pans.

X-ray powder diffraction patterns were obtained by Phillips PW3040/60 X'Pert PRO diffractometer equipped by X'Celerator detector; CuK_α radiation 1,541874Å. The 2Θ range was 4-30°, and step size was 0,0167°.

Detailed description of the invention

According to the present invention, a process for the preparation of crystalline carvedilol is performed in ethyl acetate as a crystallization solvent or ethyl acetate with added water in miscible mixtures, as a crystallization solvent.
The present invention further provides processes for crystallization, comprising dissolving carvedilol in concentrations from 1-40% w/w in heated solvents, as ethyl acetate or ethyl acetate/water mixtures, and cooling the crystallization mixtures to lower temperatures than the boiling point of the crystallization mixtures to provoke crystallization of carvedilol solid crystalline modifications.

Carvedilol could be successfully crystallized from ethyl acetate using the difference in solubility of the drug, which is higher in warm or boiling ethyl acetate and lower in cooled ethyl acetate, where at the temperature lower than 0°C, the solubility of carvedilol is lower than 0.5% w/w.

With cooling the clear carvedilol solutions in ethyl acetate to lower temperatures than the boiling point of ethyl acetate we can observe crystallization of solid material.

Crystallization of solid crystalline drug from solutions containing 25-30% w/w of carvedilol starts at temperatures higher than 60°C.
Crystallization of solid crystalline drug from solutions containing 2-10% w/w of carvedilol starts at temperatures from 20-40°C.
Crystallization of solid crystalline drug from solutions with concentrations from 10-25% w/w evidently occurs in temperature interval from 40-60°C.
If we are using the carvedilol preparation method with crystallization of the drug from solutions containing 3-30% w/w of carvedilol in ethyl acetate, pure carvedilol modification II is formed and isolated, however in some particular conditions appearance of carvedilol solvates could be detected.
By lowering the concentration of carvedilol in ethyl acetate the occurrence of ethyl acetate solvates of carvedilol is more probable.

By crystallization of carvedilol from ethyl acetate solutions in ethyl acetate at concentrations lower than 10% w/w, preferably 5% w/w and most preferably 3% w/w, the formation of carvedilol solvates is predominant.

Carvedilol prepared by crystallization from 2% w/w carvedilol ethyl acetate solution contains 12% w/w of included ethyl acetate in the crystal lattice of solid material.

The solvated form is well stable in suspension, and as well could be isolated and characterized. At ambient temperature it is only temporarily stable and in a week time it re crystallizes to more stable solid modifications.

Using the drying temperature higher than 50°C, preferably 55°C and most preferably 60°C during the drying process, at normal or reduced pressure applied, meta-stable solvated form is transformed to modification II, III or to a mixture of both modifications.

Applying vacuum drying of ethyl acetate solvates at temperatures lower than 50°C, also non-solvated carvedilol modification VII could be isolated. The modification is stable at the temperatures lower than 50°C, however it re crystallizes in solid form to more stable modification II or to the mixture of modifications II and III at higher temperatures and/or at longer storage times.

Applying drying of ethyl acetate solvates or crystalline carvedilol form VII at temperatures from 60-100°C a stable modification II could be isolated. The preferred temperature range is 70-80°C.

The present invention further provides the novel crystalline solid modification of carvedilol, non-solvated form, designated as form VII.

The non-solvated crystalline form VII is characterized by the melting point 68.8-72.4°C.

The form VII exhibits IR spectrum, Figure 1, with characteristic absorption bands at:
3469.2 cm^{-1}, 3393.5 cm^{-1}, 3345.5 cm^{-1}, 3278.1 cm^{-1}, 3054.5 cm^{-1}, 3009.0 cm^{-1}, 2909.8 cm^{-1}, 2871.2 cm^{-1}, 2836.5 cm^{-1}, 1736.2 cm^{-1}, 1625.8 cm^{-1}, 1606.3 cm^{-1}, 1589.1 cm^{-1}, 1507.6 cm^{-1}, 1452.7 cm^{-1}, 1441.4 cm^{-1}, 1383.1 cm^{-1}, 1347.5 cm^{-1}, 1332.7 cm^{-1}, 1305.0 cm^{-1}, 1284.5 cm^{-1}, 1255.6 cm^{-1}, 1226.9 cm^{-1}, 1215.0 cm^{-1}, 1178.8 cm^{-1}, 1151.6 cm^{-1}, 1123.6 cm^{-1}, 1095.8 cm^{-1}, 1040.0 cm^{-1}, 1020.9 cm^{-1}, 992.6 cm^{-1}, 957.1 cm^{-1}, 938.4 cm^{-1}, 907.0 cm^{-1}, 848.1 cm^{-1}, 798.1 cm^{-1}, 784.1 cm^{-1}, 745.0 cm^{-1}, 722.9 cm^{-1}, 621.6 cm^{-1}, 611.4 cm^{-1}, 575.9 cm^{-1}, 538.4 cm^{-1}, 483.0 cm^{-1}, 434.1 cm^{-1}.

The most characteristic absorption bands of the form VII are at: 3469.2 cm^{-1}, 3278.1 cm^{-1}, 2871.2 cm^{-1}, 1123.6 cm^{-1}, 1095.8 cm^{-1}, 745.0 cm^{-1}, 722.9 cm^{-1}.

The form VII is further characterized by DSC analysis, Figure 2. The DSC curve shows two endotherms; the first endotherm with the peak temperature at about 73°C and the second one with the peak temperature at about 114°C. The first endotherm is due to the polymorphic transition from form VII to more stable form II, the second endotherm is the melting of form II.

The crystalline form VII is further identified by XRPD analysis, Figure 3. The X-ray powder diffraction pattern of the form VII shows characteristic two-theta values at: 6.42, 6.78, 10.94, 11.58, 12.90, 13.62, 16.79, 17.51, 17.90, 18.81, 19.42, 20.83, 21.19, 21.93, 23.30, 24.49, 25.27, 26.09, 27.20, 29.21 ±0.1.

The most characteristic diffractions of the form VII are at: 6.42, 6.78, 10.94, 11.58, 12.90, 13.62, 16.79, 17.51, 17.90, 23.30 and 27.20 ± 0.1 two-theta degrees.

Our further investigation was the usage of the mixtures of ethyl acetate and water as a solvent system for re crystallization of carvedilol. Some additional interesting morphological behaviour of carvedilol was observed.

Generally, if we are using miscible solutions of ethyl acetate and water for crystallization of carvedilol, modification II, modification III and new modification IX in pure form, or in mixtures are formed.

With ethyl acetate containing no water, or quantities of water smaller than 0.8% w/w, preferably 0.6% w/w of water, modification II is isolated in pure crystalline morphological form.

If we are using ethyl acetate with contents of water between 0.8-1.5% w/w for crystallization of carvedilol, modification III in pure form or in mixtures with modification II is formed.

The mixtures of modification III and new polymorphic modification IX could be isolated using ethyl acetate with 2-3% w/w of water for re crystallization of carvedilol.

The pure new polymorphic modification IX of carvedilol is prepared using ethyl acetate and water in a miscible mixture as a solvent for crystallization. The miscible mixture of ethyl acetate and water contains preferably more than 3% w/w of water and most preferably more than 4% w/w of water.
The preferred concentration of carvedilol is from 8-25% w/w.

The present invention further provides the novel crystalline solid modification of carvedilol, designated as form IX.

The form IX is characterized by the melting point 94.5-96.2°C.

The form IX exhibits IR spectrum, Figure 4, with characteristic absorption bands at:
3568.0 cm^{-1}, 3339.1 cm^{-1}, 3287.9 cm^{-1}, 3201.4 cm^{-1}, 3052.8 cm^{-1}, 2976.3 cm^{-1}, 2942.9 cm^{-1}, 2924.3 cm^{-1}, 2896.1 cm^{-1}, 2881.7 cm^{-1}, 2860.0 cm^{-1}, 2841.4 cm^{-1}, 2714.0 cm^{-1}, 2660.6 cm^{-1}, 1911.7 cm^{-1}, 1882.4 cm^{-1}, 1664.1 cm^{-1}, 1629.7 cm^{-1}, 1607.2 cm^{-1}, 1593.5 cm^{-1}, 1506.9 cm^{-1}, 1488.0 cm^{-1}, 1470.1 cm^{-1}, 1455.5 cm^{-1}, 1443.8 cm^{-1}, 1406.1 cm^{-1}, 1386.4 cm^{-1}, 1349.9 cm^{-1}, 1334.9 cm^{-1}, 1307.9 cm^{-1}, 1288.4 cm^{-1}, 1254.0 cm^{-1}, 1227.9 cm^{-1}, 1182.8 cm^{-1}, 1148.4 cm^{-1}, 1125.4 cm^{-1}, 1104.0 cm^{-1}, 1091.2 cm^{-1}, 1051.7 cm^{-1}, 1018.6 cm^{-1}, 997.2 cm^{-1}, 930.9 cm^{-1}, 906.1 cm^{-1}, 851.5 cm^{-1}, 838.3 cm^{-1}, 816.7 cm^{-1}, 798.3 cm^{-1}, 782.7 cm^{-1}, 771.5 cm^{-1}, 751.9 cm^{-1}, 748.0 cm^{-1}, 737.1 cm^{-1}, 721.4 cm^{-1}, 657.1 cm^{-1}, 626.6 cm^{-1}, 612.9 cm^{-1}, 586.9 cm^{-1}, 567.9 cm^{-1}, 546.6 cm^{-1}, 526.5 cm^{-1}, 464.2 cm^{-1}, 449.6 cm^{-1}, 435.8 cm^{-1}, 415.8 cm^{-1}.

The most characteristic absorption bands of the form IX are at: 3568.0 cm^{-1}, 3339.1 cm^{-1}, 3287.9 cm^{-1}, 2942.9 cm^{-1}, 2896.1 cm^{-1}, 1349.9 cm^{-1}, 1307.9 cm^{-1}, 1288.4 cm^{-1}, 1104.0 cm^{-1}, 997.2 cm^{-1}, 737.1 cm^{-1}.

The form IX is further characterized also by DSC analysis.
The DSC curve of form IX (Figure 5), exhibits the minor endotherm at the peak temperature of about 80°C and the major endotherm at the peak temperature of about 99°C and the onset temperature of about 95°C.
The semi hydrated modification IX releases water from the crystal lattice at temperatures higher than 60°C (the first endotherm exhibits from DSC curve), and there formed non-hydrated modification, which is characterized by the second DSC endotherm. Up to the

melting point the non-hydrated material retains the same crystalline lattice. Exposing the non-hydrated modification to the normal ambient environment and temperatures lower than 60°C, reversible hydratation of the anhydrous form occurs and the semi hydrated modification is obtained.

The form IX is also analyzed by XRPD analysis, Figure 6. The X-ray powder diffraction pattern of the form IX shows characteristic two-theta values at: 6.16, 6.46, 8.39, 10.88, 11.39, 12.35, 12.98, 13.62, 14.72, 16.86, 17.42, 18.26, 19.28, 19.58, 21.88, 23.15, 24.61, 25.58, 26.06, 27.40, 27.63, 29.01, 29.55 ± 0.1.

The most characteristic diffractions of the form IX are at 6.16, 6.46, 11.39, 12.35, 13.62, 14.72, 16.86, 19.28, 19.58 and 23.15± 0.1 two-theta degrees.

The following examples illustrate the invention without limiting it thereto.

Examples

Example 1

Preparation of crystalline carvedilol ethyl acetate solvate

20 g of carvedilol morphological form II was dissolved in 740 ml ethyl acetate with less than 0.1% w/w of water. The mixture was heated to the temperature of the boiling point or till the solid was dissolved, and the clear reaction mixture was obtained. After heating was stopped, the reaction mixture was cooled to approximately 25°C. The solid product started to precipitate from the crystallization mixture. The crystallization mixture was further cooled to 0-5°C and after approximately 1hour the solid material was filtered off. The solid material was dried at ambient temperature 20-25°C for 6-12 hours and 16.7 g of ethyl acetate solvate of carvedilol with the melting point from 66-70°C was obtained. According to TGA analysis and ^{1}H NMR the product contained 12-13% w/w of ethyl acetate.

This example was repeated using carvedilol morphological form III, a mixture of carvedilol forms II and III or amorphous carvedilol instead of carvedilol form II. The products were all identical to the product obtained with carvedilol form II.

Example 2

Preparation of crystalline carvedilol form VII

Carvedilol ethyl acetate solvate was dried at reduced pressure 10-20 mmHg at maximum 50°C to evaporate the solvent and after loss of weight for 12 to15% in 6-8 hours, non-solvated carvedilol of morphological form VII with the melting point 68.8-72.4°C was isolated.

Example 3

Preparation of crystalline carvedilol form II

Crystalline carvedilol form II was obtained by drying carvedilol form VII at temperature 70-80°C for 6-8 hours.

Example 4

Preparation of crystalline carvedilol form IX

4 g of carvedilol morphological form II was dissolved in 26.6 ml ethyl acetate with 4% w/w of water. The mixture was heated to the temperature of the boiling point, or till the solid was dissolved, and the clear reaction mixture was obtained. After heating was stopped, the reaction mixture was cooled to 40-45°C. The solid product started to precipitate from the crystallization mixture, and heating at this temperature was maintained for 0.5-1.5 hour. After the reaction mixture was cooled gradually to 20-25°C and further to 0-5°C. At 0-5°C the crystallization mixture was stirred approximately 1hour and the solid material was filtered off. The solid material was dried at ambient temperature 20-25°C for 12 hours. 3.7 g of carvedilol was obtained. The product was dried till constant weight for approximately 2-4 hours at 50-60°C, at reduced pressure 10-30 mmHg.

3.56g, 91% of product was obtained, with the melting point 94.5-96.2°C.

This example was repeated using carvedilol morphological form III, a mixture of carvedilol forms II and III or amorphous carvedilol instead of carvedilol form II. The products were all identical to the product obtained with carvedilol form II.

Example 5

Preparation of crystalline carvedilol form IX

5 g of carvedilol morphological form II was dissolved in 32.1 ml ethyl acetate with 6.8% w/w of water. The mixture was heated to the temperature of the boiling point or till the solid was dissolved and the clear reaction mixture was obtained. After heating was stopped, the reaction mixture was cooled. The product started to precipitate from the crystallization mixture at 25-30°C. The crystallization mixture was cooled gradually to 0-5°C and after approximately 1hour the crystallization mixture was filtered off. The solid material was dried at ambient temperature, 20-25°C for 20 hours. The product was dried till constant weight for approximately 2-4 hours at 50-60°C, and at reduced pressure 10-30 mmHg.

4.74 g, 94.8% of polymorph IX was obtained, with melting point 94.5-97.3°C.

This example was repeated using carvedilol morphological form III, a mixture of carvedilol forms II and III or amorphous carvedilol instead of carvedilol form II. The products were all identical to the product obtained with carvedilol form II.

Claims

1. The crystalline carvedilol form IX, characterized by an X-ray powder diffraction pattern having peaks at: 6.16, 6.46, 11.39, 12.35, 13.62, 14.72, 16.86, 19.28, 23.15 ± 0.1 degrees two-theta.

2. The crystalline carvedilol form IX according to claim 1, wherein the X-ray powder diffraction pattern further contains the following two theta values: 6.16, 6.46, 8.39, 10.88, 11.39, 12.35, 12.98, 13.62, 14.72, 16.86, 17.42, 18.26, 19.28, 21.88, 23.15, 24.61, 25.58, 26.06, 27.40, 27.63, 29.01, 29.55 ± 0.1

3. The crystalline carvedilol form IX, characterized by the DSC curve which exhibits the minor endotherm at the peak temperature of about 80°C and the major endotherm at the peak temperature of about 99°C and the onset temperature of about 95°C.

4. The crystalline carvedilol form IX, characterized by IR spectrum with characteristic absorption bands at: 3568.0 cm^{-1}, 3339.1 cm^{-1}, 3287.9 cm^{-1}, 2942.9 cm^{-1}, 2896.1 cm^{-1}, 1349.9 cm^{-1}, 1307.9 cm^{-1}, 1288.4 cm^{-1}, 1104.0 cm^{-1}, 997.2 cm^{-1}, 737.1 cm^{-1}.

5. A process for the preparation of the crystalline carvedilol form IX, wherein carvedilol is crystallized from ethyl acetate containing more than 3% w/w of water.

6. A process for the preparation of the crystalline carvedilol form IX according to claim 5, wherein ethyl acetate contains preferably more than 4 % w/w of water.

7. A pharmaceutical composition, comprising crystalline carvedilol form IX according to any one of the preceding claims in admixture with at least one pharmaceutically acceptable excipient, diluent, or carrier.

8. A pharmaceutical composition, comprising crystalline carvedilol form IX according to any one of the preceding claims for use as a medicament.

9. The crystalline carvedilol form VII, characterized by an X-ray powder diffraction pattern having peaks at: 6.42, 6.78, 10.94, 11.58, 12.90, 13.62, 16.79, 17.51, 17.90, 20.83 and 27.20 ±0.1 degrees two-theta.

10. The crystalline carvedilol form VII according to claim 9, wherein the X-ray powder diffraction pattern further contains the following two theta values: 6.42, 6.78, 10.94, 11.58, 12.90, 13.62, 16.79, 17.51, 17.90, 18.81, 19.42, 20.83, 21.19, 21.93, 23.30, 24.49, 25.27, 26.09, 27.20, 29.21 ±0.1 degrees two-theta.

11. The crystalline carvedilol form VII, characterized by IR spectrum with peaks at: 3469.2 cm^{-1}, 3278.1 cm^{-1}, 2871.2 cm^{-1}, 1123.6 cm^{-1}, 1095.8 cm^{-1}, 745.0 cm^{-1}, 722.9 cm^{-1}.

12. The crystalline carvedilol form VII, characterized by the DSC curve with the first endotherm at the peak temperature of about 73°C and the second one at the peak temperature of about 114°C.

13. A process for the isolation of the crystalline carvedilol form VII according to claim 9, wherein ethyl acetate solvate is vacuum dried at temperatures lower than 50°C.

14. A process for the preparation of crystalline carvedilol form II, wherein crystalline carvedilol form VII or ethyl acetate solvate is dried at temperatures from 60-100°C.

15. A process for the preparation of crystalline carvedilol form II according to claim 14, wherein the preferred temperature is between 70-80°C.

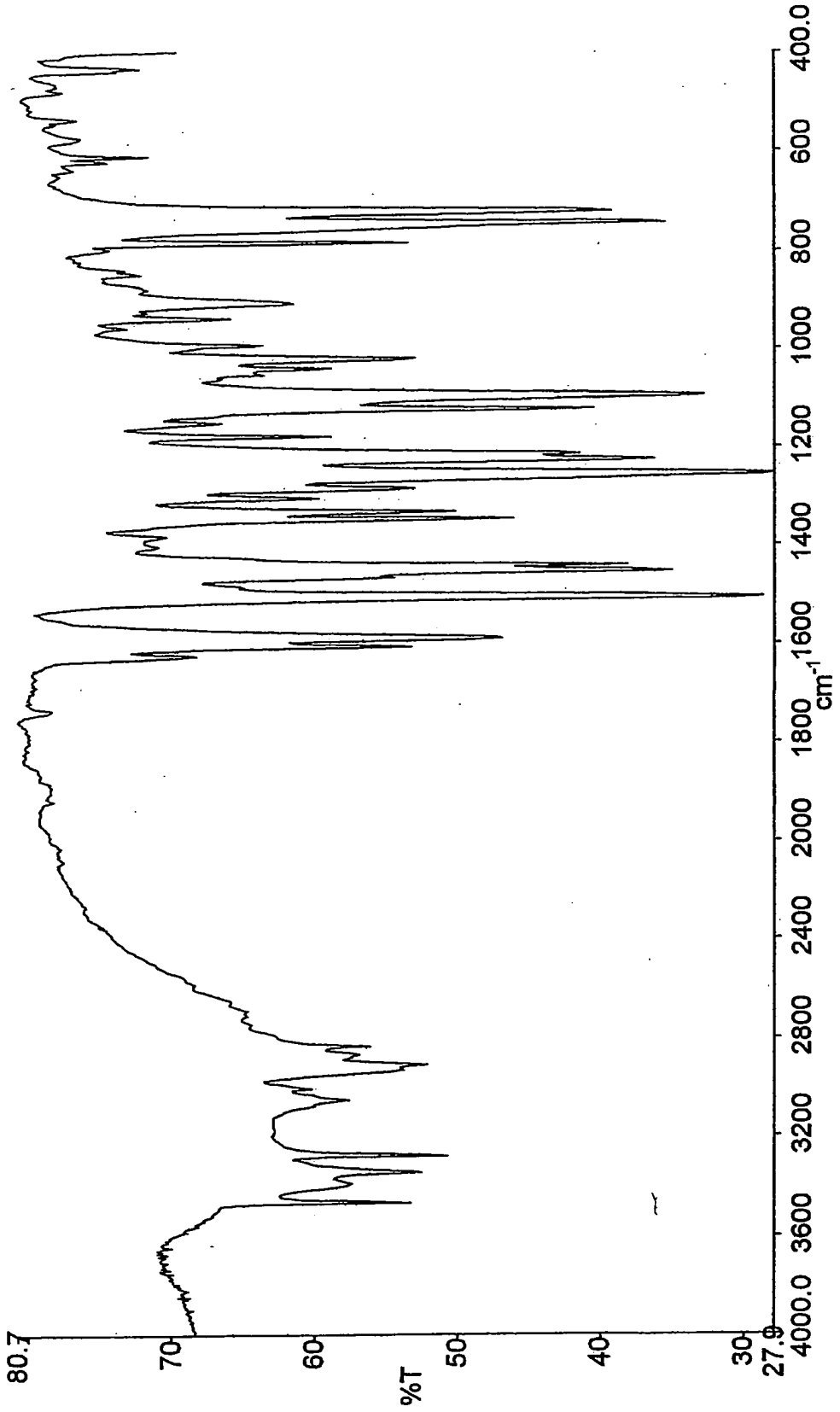

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Fig. 1

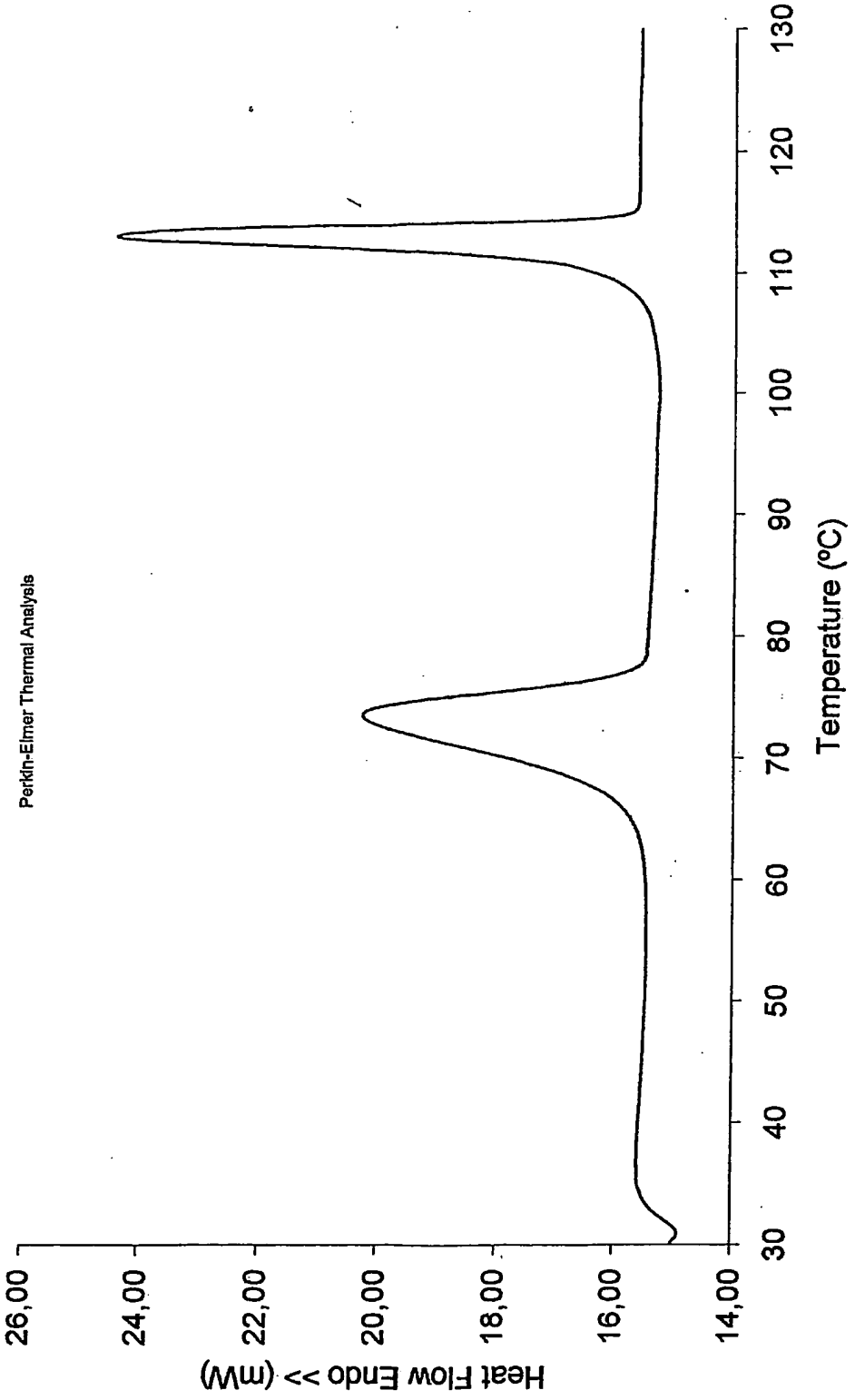
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Fig. 2

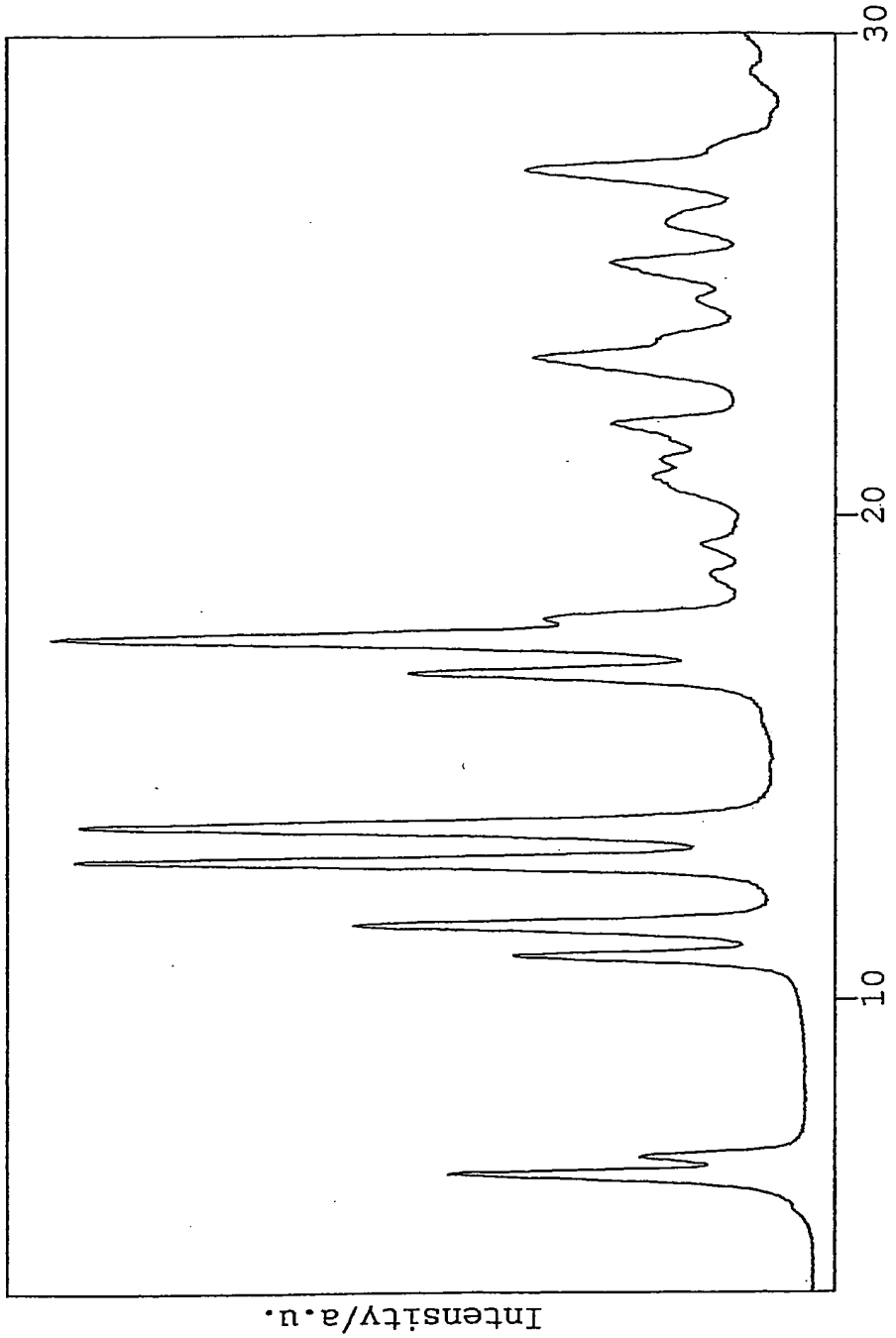

Fig. 3

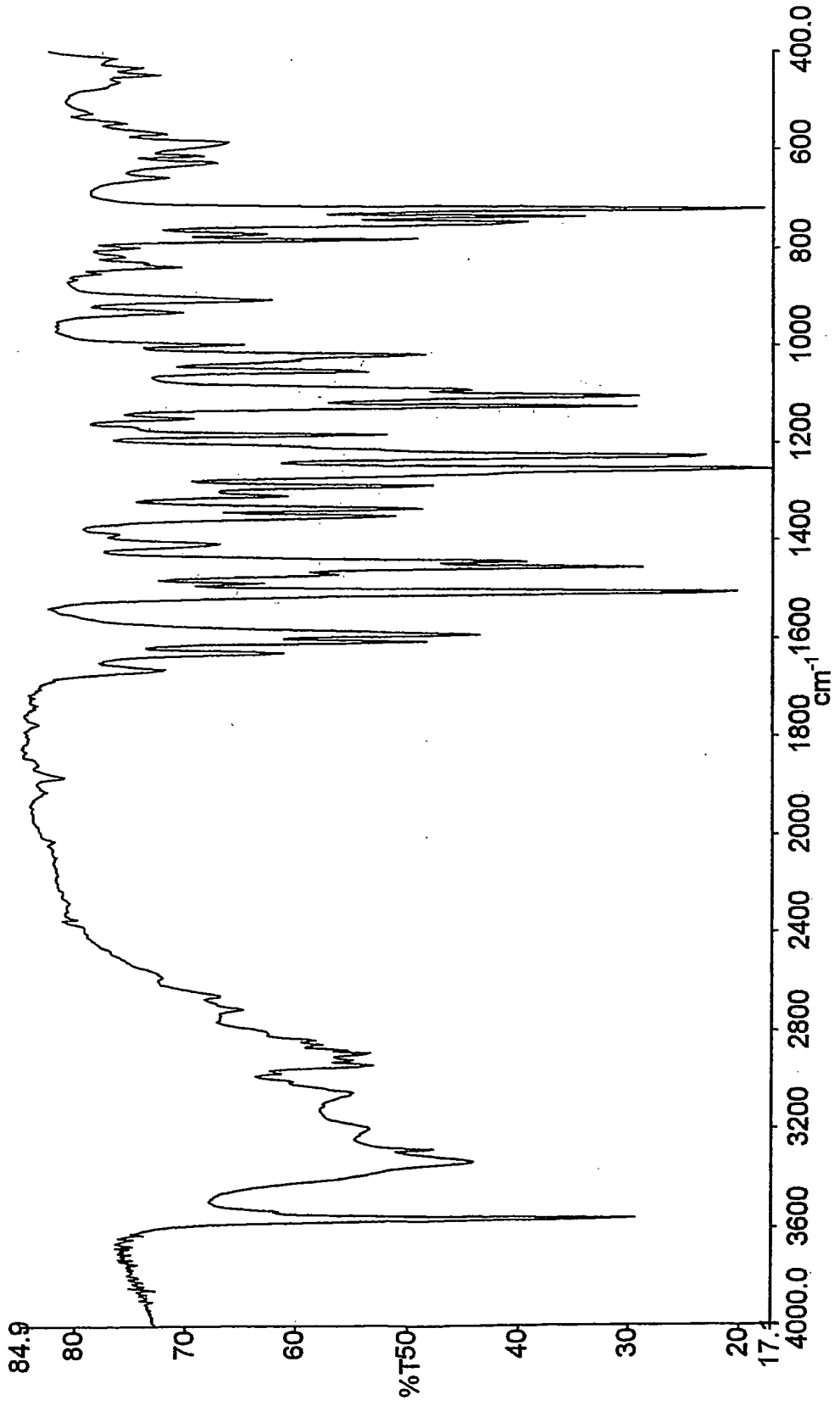
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Fig. 4

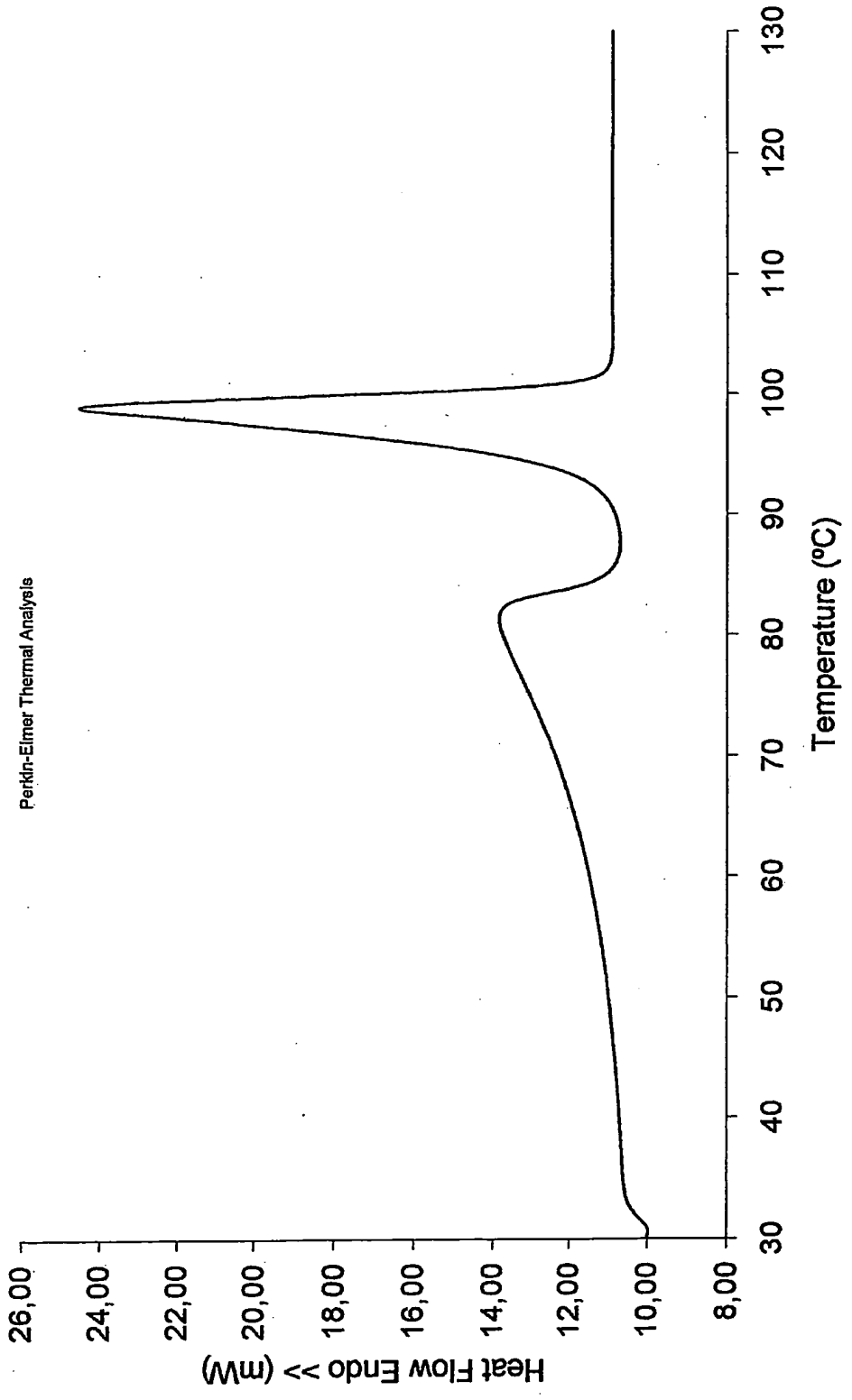
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Fig. 5

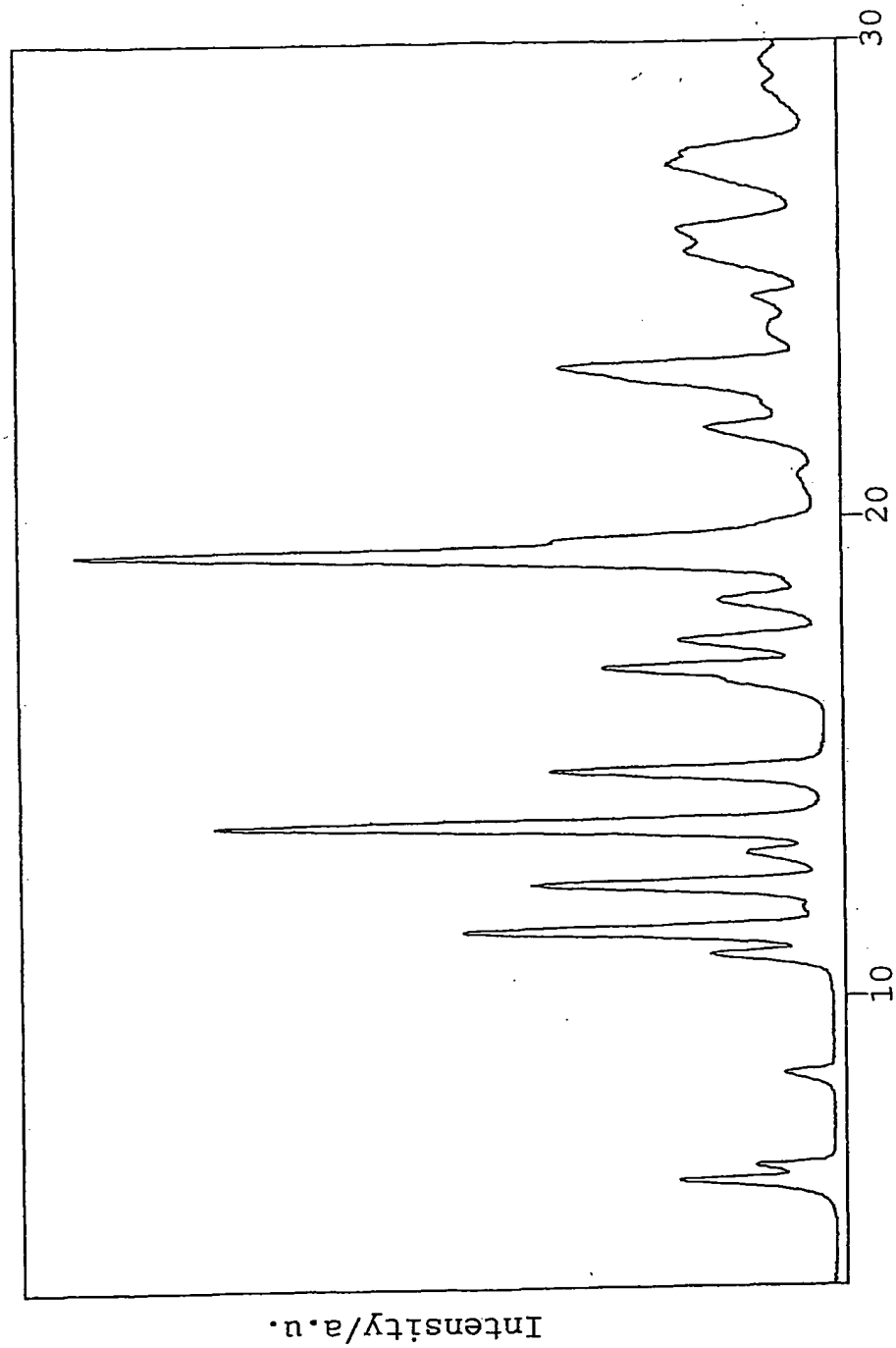

Fig. 6